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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,004	08/30/2005	George W. Muller	9516-058-999	9094

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Jones Day
222 East 41st Street
New York, NY 10017

EXAMINER

PACKARD, BENJAMIN J

ART UNIT	PAPER NUMBER
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1612

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/535,004	Applicant(s) MULLER ET AL.	
	Examiner Benjamin Packard	Art Unit 1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 47-58 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 47-58 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn as a result of the amended claims. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Note, the elected groups have been expanded to include the diseases ameliorated by the reduction of TNF-alpha claimed in the new claim 47.

Scope of Enablement Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting TNF-alpha, does not reasonably provide enablement for the prevention of the various disorders in claim 47. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).¹

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, all Wands factors have been considered and the following factors that are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative

¹ As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is “undue”, not “experimentation”.

skill level

The invention relates to the prevention of the ocular and oral diseases of claim 47. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Barnett (Journal of the American Dental Association, vol. 137(3)16S-21S, 2006), at page 17S-18S the authors explain how signs of gingivitis may not be apparent during bursts of disease activity, therefore without knowing if is occurring, it would be impossible to know if prevention is occurring. Further, gingivitis is a recurring disorder; therefore, it cannot be “prevented”.

2. The breadth of the claims

Since the instant specification provides no limiting definition of the term “prevention”, the examiner will adopt the broadest reasonable interpretation for same. Merriam-Webster Online Dictionary defines “prevention” as “to keep from happening or existing”, i.e., to completely eradicate.

The claims are thus very broad insofar as they recite the “prevention” of oral or ocular diseases of instant claim 47, i.e., the complete eradication of same. While such “prevention” might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the “real world” in which patients live; these diseases or disorders are always a risk.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for the prevention of the disorders of claim 47.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to prevent the diseases of claim 47 as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

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3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 47-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller (US 5,877,200, see Applicants IDS dated 8/31/2005 cite A52) in view of Ron et al (US 6,204,270).

Muller teaches the inhibiting effect of TNF-alpha (column 11 line 61) with enantiomerically pure (+)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro- isoindol-2-yl)-propionamide, (column 11 lines 29-33 which teaches use of each individual isomers of disclosed compounds, including column 24 lines 22-23 where 3- (3,4-dimethoxy-phenyl)-3-(1-oxoisindolin-2-yl)propionamide and 3-(3,4-dimethoxy- phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide are the same compound). Muller additionally teaches using the compound as a therapeutic strategy for other conditions where TNF-alpha is a trigger (column 2 lines 22-39). Dosages are taught between 10-500 mg (column 10 line 67-column 11 line 5).

Muller does not disclose the instantly claimed diseases.

Ron et al teaches a method of treating or preventing eye disorders by applying anti-TNF-.alpha. agents wherein the eye disorder is selected from the list of uveitis, glaucoma, keratic precipitates, retinal (macular) oedema and neovascularization,

diabetic retinopathy, bacterial, fungal and viral conjunctivitis, macular degeneration and inflammation response after intra-ocular lens implantation (claims 14-16).

Ron et al does not disclose the TNF-alpha agent instantly claimed.

One of ordinary skill in the art would find it obvious to use the TNF alpha inhibitors of the secondary reference because they share this common activity with the compounds of the primary reference, and thus would be reasonably predicted to provide corresponding therapeutic effects. See Daichi Sankyo v. Aptotex, 84 USPQ2d 1285 (Fed. Cir. 2007).

Claims 47 and 57-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller (US 5,877,200, see Applicants IDS dated 8/31/2005 cite A52, as applied to claim 47 above) in view of Ron et al (US 6,204,270, as applied to claim 47 above) and Clark et al (US 4,933,172).

Muller teaches the inhibiting effect of TNF-alpha (column 11 line 61) with enantiomerically pure (+)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro- isoindol-2-yl)-propionamide, (column 11 lines 29-33 which teaches use of each individual isomers of disclosed compounds, including column 24 lines 22-23 where 3- (3,4-dimethoxy-phenyl)-3-(1-oxoisindolin-2-yl)propionamide and 3-(3,4-dimethoxy- phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide are the same compound). Muller additionally suggests using the compound as a therapeutic strategy for other conditions (column 2 lines 22-39). Dosages are taught between 10-500 mg (column 10 line 67-column 11 line 5).

Muller does not disclose the instantly claimed diseases, nor does it disclose adding the additional agents of instant claims 57-58 for treatment of the diseases of instant claim 47.

Ron et al teaches a method of treating or preventing eye disorders by applying anti -TNF-.alpha. agents wherein the eye disorder is selected from the list of uveitis, glaucoma, keratic precipitates, retinal (macular) oedema and neovascularization, diabetic retinopathy, bacterial, fungal and viral conjunctivitis, macular degeneration and inflammation response after intra-ocular lens implantation (claims 14-16).

Ron et al does not disclose the TNF-alpha agent instantly claimed nor adding the additional agents of instant claims 57-58 for treatment of the diseases of instant claim 47.

One of ordinary skill in the art would find it obvious to try the TNF-alpha inhibitor of Muller in the method taught by Ron et al because they are both directed to conditions related to excess TNF-alpha production.

Beck et al teaches using anti-inflammatory agents to treat keratistis (claims 1, 21 and 23).

Beck et al does not disclose the addition of the TNF-alpha agent instantly claimed.

One of ordinary skill in the art would have been motivated to have combined the agents of the primary and secondary references in order to provide a third chemotherapeutic composition useful for the same purpose (treating eye diseases, such as keratistis). This position is consistent with well-established precedent holding that it is

prima facie obvious to combine compositions known to be individually useful together so as to provide a third composition for the same use. See, e.g., In re Kerkhoven, 205 USPQ 1069, 1072 (CCPA 1980).

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin Packard whose telephone number is 571-270-3440. The examiner can normally be reached on M-F 8-3:45 EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin Packard/
Patent Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612